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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/041,688	01/07/2002	Yong Hua Zhu	LOMAU.143A	5449

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EXAMINER	
GHALI, ISIS A D	

ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 03/30/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/041,688	ZHU ET AL.	
	Examiner	Art Unit	
	Isis Ghali	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 November 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8,10-12,14-18,20,22-24,26-29 and 31-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,8,10-12,14-18,20,22-24,26-29 and 31-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/23/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The receipt is acknowledged of applicants' request for RCE and amendment, both filed 11/25/2005; and IDS filed 01/23/2006.

Claims 7, 9, 13, 19, 25 and 30 have been canceled.

Claims 1-6, 8, 10-12, 14-18, 20, 22-24, 26-29, 31-34 are pending and included in the prosecution.

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/25/2005 has been entered.

Specification

2. It is noted in the first page of the specification that applicants claim priority to the subject matter disclosed in prior Application No. __/__,__, filed December 17, 2001. Applicants required to update the missing serial number.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-6, 8, 10-12, 14-18, 20, 22-24, 26-29, 31-34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The specification has failed to describe anywhere "liquid adhesive". Applicants have disclosed adhesive not in the liquid state. On page 20, lines 1-7 of the originally filed specification, applicants disclose that 2-cyanoacrylic ester monomers are liquids, while cyanoacylates used for medical use are of longer alkyl chain, i.e. butyl and octyl; and this disclosure does not support that the presently claimed butyl and octyl cyanoacrylate that have long alkyl chain are liquid. Additionally, even if the cyanoacrylate is liquid, this does not support that the adhesive composition comprising cyanoacrylate and other ingredients are also liquid specially the claimed composition comprises polyethylene glycol that is known as a thickening agent and may change the viscosity of the adhesive composition as a whole.

Furthermore, the amendments made to claims 1 and 12 have introduced new matter and applicants failed to point out support for the amendment. The expression

"protective shell" is not supported by the disclosure, applicants disclosed on page 11, line 18 "shell", not "protective shell". The expression "chemical reaction" is not supported by the disclosure, applicants disclosed on page 11, lines 20-21 that "shells block undesired reactions", not "chemical reactions". Applicants only disclosed on page 11 ,lines 11-13 that "other substances may be sensitive to the components of cyanoacrylate adhesive and as a result may undergo adverse chemical reaction", and this disclosure does not support "the shell is configured to block chemical reaction". Applicants did not disclose that "substantial premature curing of the adhesive is prevented", what applicants disclosed on page 11, lines 9-11 is "cyanoacrylate adhesive may contain reactive groups that activate the polymerization of cyanoacrylic esters, resulting in premature curing of the adhesive". Applicants did not disclose that "the microcapsules are configured to provide controlled release", applicants disclosed on page 11, lines 23-24 that "The microencapsulated antibiotics provide long-term controlled release". In addition, applicants disclosed on page 11, lines 17-18 that "antibiotics are entrapped into hydrophilic gelatin microcapsules", while claims 1 and 12 do not recite gelatin, and nowhere applicants disclosed antibiotics encapsulated in other types of microcapsules.

For the purpose of prosecution, claims 1 and 12 will be examined as an adhesive composition and not as "liquid adhesive". Claim 1 will be prosecuted from line 1 till the word "rate" on line 6 of the claim, and claim 12 will be examined from line 1 till the word "wound" on line 6 of the claim, and line 10, i.e. new matter are excluded till applicants point out to the support, MPEP 7.14.02.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 1-5, 8, 12, 14-17, 20, 27-29, 32-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 96/10374 ('374) in view of US 6,207,193 ('193).

WO '374 discloses *in situ* polymerizing (*in situ* curing) biomedical implant material and a method for repair of mammalian tissue using the same biomedical material (abstract; page 8, line 35; page 9, line 1). The material comprises cyanoacrylate adhesive, hydrophilic porosifying agent and antibiotic (page 6, lines 9, 16-

17; page 7, line 1; page 8, line 23 till page 9, line 2). The hydrophilic porosifying agent includes polyethylene glycol that dissolve *in situ* as a result of exposure to an aqueous environment, e.g. body fluids are aqueous (page 4, lines 20-23). The *in situ* polymerizing implant material is introduced into the repair site (reads on wound) by variety of means and is used as a sealant in anatomic regions where it would be difficult to use a pre-cast dressing (page 12, lines 12-19). Introducing the *in situ* polymerizing implant material into the repair site reads on the step of "approximating the wound" in claim 12. Polymerization *in situ* reads on the step of curing the adhesive in claim 12. The adhesive material is a liquid as implied by its application at the site by pouring (page 12, lines 12-15).

The reference does not teach encapsulating the active substance. Although the reference teaches that the porosifying agent dissolves in the aqueous environment, i.e. the body fluid, however, the reference does not teach the delivery of the substance to the tissue.

It is implied from the teaching of the reference that an active agent is delivered, such as anti-microbials including penicillin (page 12, lines 22-30). It is expected from the implanted composition that polymerizes *in situ* and comprises hydrophilic pore forming agent and active substance, to deliver the substance through the pores after the pore-forming agent dissolves.

US '193 teaches transdermal drug delivery device wherein a drug or a therapeutic agent, such as antibiotics, is encapsulated in water soluble carbohydrate and suspended in butyl or octyl cyanoacrylate ester to provide time release transdermal

drug delivery system (abstract; col.2, lines 40-41, 63-64; col.3, lines 35-36). The butyl and octyl cyanoacrylate esters are inert with respect to the capsule material and active agents so that no interaction between them even when exposed to moisture (col.3, lines 45-50).

The combined teachings of the references do not teach specific antibiotics as claimed in claims 27-29 and 32-34. In any event applicants failed to superior and unexpected results that are achieved from using those specific antibiotics, and they do not impart patentability to the claims, absent evidence to the contrary.

Accordingly, it would have been obvious to one having ordinary skill in the art at the time of the invention to provide a composition and a method for sealing wound by applying adhesive composition comprising cyanoacrylate, pore forming agent and antibiotic as disclosed by WO '374, and select butyl or octyl cyanoacrylate and further encapsulate the antibiotic as disclosed by US '193, motivated by the teaching of US '193 that butyl and octyl cyanoacrylate are inert with respect to the capsule material and the active agent, and motivated by the teaching of US '193 that encapsulated active agent provides time release transdermal delivery of the active agent, with reasonable expectation of having adhesive wound sealing composition that is inert and comprises butyl or octyl cyanoacrylate, pore forming agent and encapsulated antibiotic to deliver the antibiotic to the wound in a controlled manner to prevents sepsis of the wound and its subsequent drawbacks.

8. Claims 10, 11, and 22-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO '374 in view of US '193 and further in view of WO 96/00760 ('760).

The teachings of WO '374 in view of US '193 are discussed above.

However, WO '374 in view of US '193 do not teach the anti-degradation agents claimed in claims 10, 11, 23 and 24; or the wound as a lacerated wound as in claim 22.

WO '760 teaches a biocompatible composition comprising pH modifier and butyl and octyl cyanoacrylate monomer wherein the composition is useful as biomedical and surgical adhesive and sealant that finds uses in repairing traumatically lacerated tissues, as claimed by present claim 22 (abstract; page 4, lines 6-12; page 5, line 17). In presence of blood, the composition has adequate flexibility and strength to withstand normal movement of the tissue and a bond strength that is maintained as natural tissue healing proceeds (page 6, lines 15-19; page 18, lines 23-32). The pH modifier regulates the polymer biodegradation by regulating the pH of the in vivo environment of the biocompatible composition and makes it proceeds more slowly than it does at a physiological pH, this reads on anti-degradation agents presently claimed in claims 10 and 23, resulting in retarding the rate of release of the degradation products, thereby reducing their toxic effects (page 3, lines 27-29; page 9, lines 28-35). PH modifiers include ascorbic aid (vitamin C), presently claimed in claims 11 and 24 (page 10, line 26). The compositions of the reference

Accordingly, it would have been obvious to one having ordinary skill in the art at the time of the invention to provide composition and method for sealing the wound using

adhesive composition comprising octyl or butyl cyanoacrylate, pore forming agent and encapsulated antibiotic as disclosed by WO '374 in view of US '193 and add anti-degradation agents such as vitamin C disclosed by WO '760 to the sealant composition disclosed by of WO '374 in combination with US '193 motivated by the teaching of WO '760 that the cyanoacrylate composition comprising degradation retarding vitamin C has adequate flexibility and strength in presence of blood to withstand normal movement of the tissue and has a bond strength that is maintained as natural tissue healing proceeds, and able to regulate the polymer biodegradation and make it proceeds more slowly than it does at a physiological pH resulting in retarding the rate of release of the degradation products and makes the adhesive useful tissue sealant that find uses in traumatically lacerated tissues, a function desired by applicants, with reasonable expectation of having safe, inert, strong and flexible wound sealant that comprises butyl or octyl cyanoacrylate, pore forming agent, encapsulated antibiotic and vitamin C which regulates the polymer biodegradation and make it proceeds more slowly resulting in an adhesive useful for traumatically lacerated wounds.

9. Claims 6 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO '374 in view US '193 and further in view of WO 99/20685 ('685).

The teachings of WO '374 in view of US '193 are discussed above.

However, the combined teachings of WO '374 in view of US '939 does not teach the molecular weight of the polyethylene glycol as claimed in claims 6 and 18.

WO '685 teaches a formulation that forms a film comprising water soluble pore forming agent such as polyethylene glycol that leaches out through the film *in situ* and creates a perforations that regulate the release rate of active agents (page 7, lines 10-16). The preferable molecular weight of the polyethylene glycol that is able to create adequate pore size for controlling the release of the active agents is from 540 to 8000, i.e. encompasses the molecular weight claimed by applicants in claims 6 and 18 (page 9, lines 23-28; page 10, lines 1-2).

Accordingly, it would have been obvious to one having ordinary skill in the art at the time of the invention to provide composition and method for sealing the wound wherein the composition comprises butyl or octyl cyanoacrylate, polyethylene glycol as pore forming agent and encapsulated antibiotics as disclosed by WO '374 in view of US '193 and select the molecular weight of the polyethylene glycol between 540 and 8000 as taught by WO '685 because this range of molecular weight is preferred because of the ability of polyethylene glycol having such molecular weight to create adequate pore size for controlling the release of the active agents, with reasonable expectation of success of having wound sealant composition comprising butyl or octyl cyanoacrylate, polyethylene glycol with molecular weight ranging from 540 to 8000 as pore forming agent and encapsulated antibiotics wherein the polyethylene glycol creates pores of adequate sizes for controlling the release of antibiotics to the treated wound.

10. Claims 26 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO '374 in view of US '193 and further in view of US 5,695,779 ('779).

The teachings of WO '374 and US '193 are discussed above.

However, the combined teachings of the references do not teach microcapsule comprises gelatin.

US '779 teaches transdermal drug delivery system wherein the delivery of the drug is controlled by encapsulating the drug in water-soluble microcapsule comprising gelatin (abstract; col.3, lines 1-4; col.4, lines 61-62; col.5, lines 1-3).

Accordingly, it would have been obvious to one having ordinary skill in the art at the time of the invention to provide composition and method for sealing the wound using adhesive composition comprising octyl or butyl cyanoacrylate, pore forming agent and encapsulated antibiotic as disclosed by WO '374 in view of US '193, and select gelatin as a material for the microcapsule as disclosed by '779, motivated by the teaching of US '779 that gelatin is water soluble and therefore provides controlled release of the active agent from transdermal drug delivery device, with reasonable expectation of having adhesive wound sealing composition that is inert and comprises butyl or octyl cyanoacrylate, pore forming agent and antibiotic encapsulated in gelatin microcapsule to deliver the antibiotic to the wound in a controlled manner to prevents sepsis of the wound and its subsequent drawbacks.

Response to Arguments

11. Applicant's arguments with respect to claims 1-6, 10-12, 14-18, 20, 22-24, 26-29, 31-34 have been considered but are moot in view of the new ground(s) of rejection.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Isis Ghali whose telephone number is (571) 272-0595. The examiner can normally be reached on Monday-Thursday, 7:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman Page can be reached on (571) 272-0602. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Isis Ghali
Examiner
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IG

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PATENT EXAMINER